(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 578 823 A1**

(12) **EUROPEAN PATENT APPLICATION published in accordance with Art. 158(3) EPC**

(21) Application number: **92907987.9**

(22) Date of filing: **06.04.92**

(86) International application number: **PCT/JP92/00420**

(87) International publication number: **WO 92/17209 (15.10.92 92/26)**

(51) Int. Cl.[5]: **A61K 47/42**, A61K 9/20, A61K 37/66

(30) Priority: **08.04.91 JP 74990/91**
08.04.91 JP 74991/91

(43) Date of publication of application: **19.01.94 Bulletin 94/03**

(84) Designated Contracting States: **AT BE CH DE DK ES FR GB GR IT LI LU NL SE**

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(54) **POROUS SOLID PREPARATION CONTAINING PHYSIOLOGICALLY ACTIVE PROTEIN SUBSTANCE.**

(57) A porous solid preparation for buccal or peroral administration, comprising a physiologically active protein substance as an active ingredient, collagen and water-soluble additives and having an excellent disintegrability.

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FIELD OF THE INVENTION

The present invention relates to a solid pharmaceutical formulation for buccal or oral administration which contains a proteinaceous physiologically active substance as an active ingredient, as well as collagen and a water-soluble additive, said formulation being characterized by being porous and having a good disintegration property, and to a preparation thereof.

THE PRIOR ART

Development of biotechnology, in particular, genetic recombination and cell culture technology has provided and will be providing substantial amount of proteinaceous physiologically active substances such as cytokines and proteinaceous hormones, for the purpose of the treatment and diagnosis in medical and animal industries

Such proteinaceous physiologically active substances are usually administered via injection, because they have, in general, poor absorption in digestive tracts.

There is a report which demonstrates that buccal administration of a little amount (2 IU/kg/day) of interferon, proteinaceous physiologically active substance, to patients suffering from a disease caused by human immunodeficiency virus type 1 (HIV-1), which is called AIDS, resulted in an improvement in its symptom (Davy K. Koech et al., Mol. Biother. Vol.2, 91-95 (1990)). WO88/03411 describes a method of contacting an interferon to the buccal cavity and the pharyngeal mucosa.

Also, a sustained release formulation which contains interferon and collagen is described in the Japanese Patent Publication (kokai) No. 97918/1985.

However, any stable solid formulations have not yet been known, which can be administered in a form for a buccal or oral route, and which can release proteinaceous physiologically active substances in an amount and over a time necessary for treating the diseases.

DESCRIPTION OF THE PRESENT INVENTION

The inventors of the present invention have completed the invention by making efforts to find the above-noted ideal formulation.

Specifically, the present invention relates to a stable solid pharmaceutical formulation which can be administered in the form suitable for a buccal or oral route, and which can release the proteinaceous physiologically active substances in an amount and over a time necessary for treating the disease, as well as a preparation thereof. More specifically, the present invention relates to a solid pharmaceutical formulation for buccal and oral administrations, which contains a proteinaceous physiologically active substance as an active ingredient, as well as collagen and a water-soluble additive, said formulation being characterized by being porous and having a good disintegration property, and to a preparation thereof.

In one embodiment, the present invention relates to a pharmaceutical formulation for treating AIDS, or for preventing the progress of AIDS, when it contains interferon as a proteinaceous physiologically active substance.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a time-course of a release of interferon from the spongy formulation of the present invention (Example 1).

Figure 2 shows a release of interferon from the collagen needle pellet as a control.

DESCRIPTION OF THE PREFERRED EMBODIMENTS FOR CONDUCTING THE PRESENT INVENTION

As shown above, the present invention relates to a solid pharmaceutical formulation for buccal and oral administrations, which contains a proteinaceous physiologically active substance as an active ingredient, as well as collagen and a water-soluble additive, said formulation being characterized by being porous and having a good disintegration property, and to a preparation thereof.

Collagen

"Collagen" which can be used in the invention includes, for example, atelocollagen which is derived from a natural resource, and which is free of a telopeptide which is an antigenic portion of collagen;

chemically modified atelocollagen; naturally-occurring collagen, and so on. The collagen which has been chemically derived from the atelocollagen includes, for example, a succinylated collagen, a methylated collagen, and so on. The naturally-occurring collagen includes, for example, a collagen from a skin of bovine, a chorda of bovine, a bowel of porcine and sheep, a human placenta, and so on.

Alternatively, the collagen which is used in the solid formulation of the present invention may be commercially available products. The commercially available products of the collagen usually contain a buffer such as phosphate buffer, citrate buffer, acetate buffer, a stabilizer, and so on. The solid formulation of the invention can contain such buffer or stabilizer.

Water-soluble additive

"Water-soluble additive" which is used in the solid formulation of the invention may be a water-soluble pharmaceutical additive which is usually used, and includes, for example, proteins, glycoproteins, amino acids, polyamino acids, peptides, saccharides, water-soluble polysaccharides, or a combination thereof. Proteins include, for example, gelatin, albumin, and so on. Glycoproteins include, for example, globulin, and so on. Amino acids include, for example, aspartic acid, arginine, glycine, leucine, and so on. Polyamino acids and peptides include, for example, polyalanine, polyglycine, sodium polygultamate, sodium polyaspartate, polylysine, polyleucine, and so on. Saccharides, polysaccharides, and water-soluble polysaccharides include, for example, fructose, sucrose, lactose, dextran, cyclodextran, mannitol, sorbitol, and so on.

Proteinaceous physiologically active substances

"Proteinaceous physiologically active substances" include, for example, simple proteins, conjugated proteins, derived proteins. In particular, such substances include, for example, a cytokine having activity for modulating immunity, an endocrine-related substance, a proteinaceous hormone, a growth factor, a nutrition factor, an enzyme, and so on, and, more particularly, include interferon, interleukin, colony stimulating factor, macrophage activating factor, and so on. Interferons include interferon-α, interferon-β, interferon-γ, and so on. Interleukins include interleukin-1, interleukin-2, and so on. Colony stimulating factors include multipotency colony stimulating factor (multi-CSF), granulocyte-monocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), monocyte macrophage colony stimulating factor (M-CSF), and so on.

The proteinaceous physiologically active substances which are used in the solid formulation of the present invention can be any substances, regardless of the preparation therefor, and include an extract from organisms, a synthetic product, a substance from a genetic recombination, a substance from a cell culture.

Alternatively, the proteinaceous physiologically active substances which are used in the solid formulation of the present invention may be commercially available products. The commercially available products of the substances usually contain some additives. The solid formulation of the invention can contain such additives. Such additives are human serum albumin, amino acid, sodium chloride, and so on, in the case of an interferon. When the proteinaceous physiologically active substance is colony stimulating factor, such additives are for example a saccharide, a sugar alcohol, polyethylene glycol. In the case of interleukins, such additives are phosphate buffer, human serum albumin, and so on.

Pharmaceutical additives

The solid formulation can contain a pharmaceutical additive, if necessary. Such "pharmaceutical additives" include any additives which are usually used, and include, for example, a stabilizer, a preservative, a buffer, a sweetener, a flavor, a binder, a suspending agent, a disintegrator, and so on.

A stabilizer includes one which is used for the proteinaceous physiologically active substances, and, in particular, albumin, gelatin, mannitol, trehalose, and so on. A preservative includes, for example, *p*-hydroxybenzoates, sorbic acid, salicylic acid, and so on. A buffer includes citrate buffer, acetate buffer, phosphate buffer, and so on. A sweetener includes, for example, mannitol, glucose, maltose, starch, lactose, and so on. A flavor includes, for example, aspartic acid, citric acid, lactic acid, and so on. A binder includes, for example, methylcellulose, ethylcellulose, carboxy methyl cellulose, and so on. A suspending agent includes, for example, Tween 20, Tween 80, and so on. A disintegrator includes, for example, glycerol, starch, and so on.

Effect of the present invention

As stated above, the solid formulations are porous. When the formulations are administered into the buccal cavity, it will disintegrate and/or dissolve to release the proteinaceous physiologically active substances, since a saliva penetrates the formulation through the pores or chinks therein. At the same time, the water-soluble additives dissolve, and the collagen matrix also disintegrates and/or dissolves, to release the proteinaceous physiologically active substances.

The present invention provides the solid formulation which can release a therapeutically-effective amount of the proteinaceous physiologically active substances at a disintegration and/or dissolution rate suitable for the buccal and oral administrations.

The solid formulations of the present invention have good disintegration property. When the solid formulation is administered to the buccal cavity, the formulation disintegrates and/or dissolves in the cavity gradually so as to release the proteinaceous physiologically active substances. In the oral administration, the formulation disintegrates and/or dissolves in digestive tracts such as esophagus, stomach, and bowel, etc., to release the proteinaceous physiologically active substances.

Further, it is possible to control a disintegration time of the solid formulation of the present invention, and to control a release amount and a release rate of the proteinaceous physiologically active substances from the formulation. Specifically, the release amount and the release time of the proteinaceous physiologically active substances can be readily modified to desired ones by changing the composition or the preparation method of the solid formulations.

As would be obvious from the above, it is easy to prepare a homogeneous formulation, because the formulation is prepared by mixing the components in the form of solutions. Accordingly, one feature of the present invention is a constant release of the proteinaceous physiologically active substances, which is particularly suitable for therapeutical use.

When the solid formulation is administered to the buccal cavity, the formulation absorbs water in the cavity, swells, and assumes viscosity, whereby it adheres to the buccal cavity, and remains therein. Thus, the solid formulation of the invention can be readily maintained in the buccal cavity, and, therefore, the proteinaceous physiologically active substances which is released from the formulation can be readily contacted to the mucosa of the cavity and the pharyngeal mucosa for enough time necessary to the treatment. The solid formulation gives no bad feeling and irritation to buccal cavity.

It is possible to make the solid formulations of the present invention in both small and large scale by the process stated above, and additionally, the solid formulations can be provided in association with good homogeneousness, good reproduction, and high yield. The process of the invention does not require special temperature and pressure in the preparation of the solid formulations. Accordingly, the process of the present invention can be applied to a labile, proteinaceous physiologically active substance to prepare a solid formulation containing such substance.

The following examples are provided to further illustrate the formulation of the present invention. Such examples are representative only and should not be construed as limiting the scope of the invention in any respect.

Examples

Example 1

A liquid mixture containing interferon-α was prepared by mixing completely 120 g of 2 % solution of atelocollagen in water, 120 g of 4 % solution of gelatin in water, 2.4 g of sucrose, and 80,000 IU of interferon-α. Each 0.3 ml portions of the liquid mixture was placed into pockets in PTP molded sheet (SUMILITE^{R}VSS-1202, a pocket: 10 mm in diameter, 0.35 ml in volume), and lyophilized on a vacuum freeze dryer R2L-30KWS type (Kyowa Shinku). After lyophilization, heat-sealing was conducted with an aluminum foil. The tablets were packed with the PTP packing sheet and the sheet was cut into fragments, each containing 10 tablets.

The resultant tablets each contain 100 IU of interferon-α (1,000 IU of interferon-α corresponds to 10 ng).

Example 2

A liquid mixture containing interferon-α was prepared by mixing completely 120 g of 2 % solution of atelocollagen in water, 120 g of 4 % solution of gelatin in water, 2.4 g of sucrose, and 160,000 IU of interferon-α. Each 0.3 ml portions of the liquid mixture was placed into pockets in PTP molded sheet

(SUMILITE^{R}VSS-1202, a pocket: 10 mm in diameter, 0.35 ml in volume), and lyophilized on the vacuum freeze dryer R2L-30KWS type (Kyowa Shinku). After the lyophilization, heat-sealing was conducted with an aluminum foil. The tablets were packed with the PTP packing sheet and the sheet was cut into fragments, each containing 10 tablets.

The resultant tablets each contain 200 IU of interferon-α.

Example 3

A liquid mixture containing interferon-α was prepared by mixing completely 120 g of 2 % solution of atelocollagen in water, 120 g of 4 % solution of gelatin in water, 2.4 g of sucrose, and 800,000 IU of interferon-α. Each 0.3 ml portions of the liquid mixture was placed into wells in microwell plate (the volume of the well: 0.35 ml), and then, dried under reduced pressure, to yield the tablets in hemi-globular forms, each of which contains 1000 IU of interferon-α.

Example 4

An aqueous solution (120 ml) was prepared, of which 0.3 ml portions contain 1000 IU of interferon-α, 3 mg of atelocollagen, 6 mg of gelatin, 3 mg of human serum albumin, 3 mg of sucrose. Each 0.3 ml portions of the liquid mixture was placed into wells in microwell plate (the volume of the well: 0.35 ml), and then, lyophilized on the vacuum freeze dryer R2L-30KWS type (Kyowa Shinku), to yield the tablets in the form of hem-globular, each of which contains 1000 IU of interferon-α.

Example 5

An aqueous solution (30 ml) was prepared, of which 0.3 ml portions contain 20 IU of erythropoietin, 3 mg of atelocollagen, 6 mg of gelatin, and 3 mg of glucose. The mixture was treated in a procedure similar to that of Example 3 to yield the formulations, each of which contains 20 IU of erythropoietin.

Example 6

An aqueous solution (12 ml) was prepared, of which 0.3 ml portions contain 2 μg of epidermal growth factor (EGF), 3 mg of atelocollagen, 6 mg of gelatin, and 3 mg of lactose. Each 0.3 ml portions of the mixture was placed into pockets in PTP molded sheet (SUMILITE^{R}VSS-1202, a pocket: 10 mm in diameter, 0.35 ml in volume), and lyophilized in a procedure similar to that of Example 1 to yield the formulations, each of which contains 2 μg of EGF.

Example 7

An aqueous solution (12 ml) was prepared, of which 0.3 ml portions contain 2 μg of epidermal growth factor (EGF), 3 mg of atelocollagen, 6 mg of gelatin, and 3 mg of lactose. The mixture was treated in a procedure similar to that of Example 4 to yield the formulations, each of which contains 2 μg of EGF.

Example 8

An aqueous solution (18 ml) was prepared, of which 0.3 ml portions contain 200 μg of GM-CSF, 6 mg of a methylated collagen, 6 mg of dextran (40), 3 mg of human serum albumin, and 3 mg of maltose. The mixture was treated in a procedure similar to that of Example 4 to yield the formulations, each of which contains of 200 μg of GM-CSF.

Example 9

An aqueous solution (120 ml) was prepared, of which 0.3 ml portions contain 1 IU of human growth hormone, 6 mg of a succinylated collagen, 3 mg of sodium polyglutamate, 3 mg of glycine, and 3 mg of mannitol. The mixture was treated in a procedure similar to that of Example 4 to yield the formulations, each of which contains of 1 IU of human growth hormone.

Example 10

A liquid mixture containing interferon-α was prepared by mixing completely 18 g of 2 % solution of atelocollagen in water, 6 g of 10 % solution of gelatin in water, 0.36 g of glucose, and 120,000 IU of interferon-α. The mixture was placed into plastic laboratory dish which have 12 cm of diameter, and then, the dishes were left stand for 7 days at room temperature. The dried products were cut into the slices having sizes of 10 mm x 10 mm, to yield the formulation in the filmy form, each of which contains about 1,000 IU of interferon-α.

Example 11

Thirty g of 2 % solution of atelocollagen in water, 8.46 ml of a solution (70.9 mg/ml) of human serum albumin in water, 0.3 g of glucose, and 0.107 ml of a solution of interferon-α in water (2 millions IU/ml) were mixed, and the mixture was lyophilized. After the lyophilized products were swelled by adding a small amount of a distilled water thereto, an additional distilled water was added to the products until the final concentration of the solid reached 29%. The mixture was fully stirred in a mortar to give a homogeneous mixture. The mixture was placed into a 10 ml disposable syringe, and centrifuged at 10,000 G for 60 minutes so that the mixture was degassed. A membrane of Gore-Tex^{R} (porous tetrafluoroethylene) was immobilized on a U-shaped aluminum material. The centrifuged mixture of the solid at 29% concentration obtained above was pushed out from the nozzle having 1.7 mm i.d., to place on the Gore-Tex^{R} membrane linearly. The linear products were carefully placed in a sloping condition into a desiccator where the relative humidity was kept 75%, and dried for 72 hours in a refrigerator, and then further dried for 24 hours in the desiccator containing silica gel.

The resultant dried products was cut into pieces having suitable length, to yield needle pellets having 0.9 mm diameter, each of which contains 1,000 IU of interferon-α.

Example 12

The formulations of the present invention have an ability to keep the active component stable. In this example, a stability test was conducted using the formulation of Example 1, which was prepared by applying the present invention to interferon-α.

Three sheets of the PTP packing formulations, which were prepared in Example 1 were kept at 40 °C in a thermostat. Each one sheet of them was removed from the thermostat at 0.5, 1 and 2 months after starting the experiment, and the contents of interferon-α in the formulations were quantified by a method provided below. The content of interferon-α at the beginning of the experiment was quantified and the contents at any later stage representing residual contents were expressed with percentage (%) when the initial content is assumed as 100.

Content quantification

Three of 10 tablets in one sheet were picked up, and each of them was added to 5 ml of the RIA buffer (PBS buffer containing 0.5% human serum albumin, and 0.01% sodium azide), and the mixtures were kept as they were for 20 hours at room temperature. Then, the mixtures were warmed at 37 °C for 5 minutes, and mixed with shaking to yield homogeneous solutions. The concentrations of interferon-α in the mixtures were determined by RIA, and the content in each one of three tablets was calculated. The resultant three values were averaged to obtain data. RIA was conducted according to the known method, using RIA kit (interferon-α RIA kit) from DAINABOT Co.

The test results are shown in Table 1. From the data, it is suggested that the formulations of the present invention have long term stability.

for 24 hours. The resultant dried products were placed in an atmosphere of an ammonia gas to neutralize, and air-dried. Then, the dried product was cut into pieces having a suitable length, to yield homogeneous needle pellets having 1 mm ± 2 % diameter, each of which contains 100,000 IU of interferon-α. Thus, the needle pellets are different from the formulation of the present invention in that the formers are prepared from a solution having higher concentration of the carrier, collagen.

Each of the formulations was added to 1.5 ml of a test solution (PBS buffer containing 0.5% human serum albumin, 0.01% sodium azide), and the mixture was stirred at room temperature. The time-course of the concentration of interferon-α in the mixture was determined by RIA.

The results are shown in Figures 1 and 2. In the figures, the vertical axis shows the release ratio of interferon-α (unit: %), and the horizontal axis shows the time (unit: minutes or days). Figure 1 shows the results of the spongy formulations of the present invention, and Figure 2 shows the results of the collagen needle pellets of the reference.

From the data, it is obvious that the release rate of the active ingredient in the spongy formulation of the present invention is faster than that of the collagen needle pellet.

Claims

1. A solid formulation for buccal or oral administration which contains a proteinaceous physiologically active substance as an active ingredient, as well as collagen and a water-soluble additive, said formulation being characterized by being porous and having a good disintegration property.

2. The solid formulation of Claim 1 wherein the proteinaceous physiologically active substance is interferon.

3. The solid formulation of Claim 1 or 2 wherein the weight ratio between collagen and water-soluble additive is 1:9 to 9:1.

4. The solid formulation of Claim 1 or 2 wherein the weight ratio between collagen and water-soluble additive is 1:9 to 1:1.

5. The solid formulation of Claim 1 or 2 wherein the density of the formulation is in the range between 0.1 mg/cm^3 and 1 g/cm^3.

6. The solid formulation of Claim 1 or 2 wherein the porosity of the formulation is in the range between 99% and 23%.

7. The solid formulation of Claim 1 or 2 wherein the disintegration time of the formulation is within 2 hours.

8. The solid formulation of Claim 1 or 2 wherein the disintegration time is in the range between 1 minute and 30 minutes.

9. A process for preparing a solid formulation for buccal or oral administration which contains a proteinaceous physiologically active substance as an active ingredient, as well as collagen and a water-soluble additive, said formulation being characterized by being porous and having a good disintegration property, which process comprises drying a liquid mixture containing the proteinaceous physiologically active substance, the collagen, and the water-soluble additive.

10. The process of Claim 9 wherein the proteinaceous physiologically active substance is interferon.

11. A solid formulation for treating AIDS, which is suitable for buccal or oral administration, and which contains interferon as an active ingredient, as well as collagen and a water-soluble additive, said formulation being characterized by being porous and having a good disintegration property.

12. A solid formulation for preventing the progress of AIDS, which is suitable for buccal or oral administration, and which contains interferon as an active ingredient, as well as collagen and a water-soluble additive, said formulation being characterized by being porous and having a good disintegration property.